

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 645	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/DK2004/000875	International filing date (day/month/year) 16.12.2004	Priority date (day/month/year) 16.12.2003
International Patent Classification (IPC) or national classification and IPC A61K31/404, A61P25/28		
Applicant LEO PHARMA A/S et al		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 25.08.2005	Date of completion of this report 22.11.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Bonzano, C Telephone No. +31 70 340-	



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International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-145 as originally filed

Claims, Numbers

1-52 as originally filed

Drawings, Sheets

1/7-7/7 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 32-62

because:

☒ the said international application, or the said claims Nos. 32-62 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-62
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-62
Industrial applicability (IA)	Yes: Claims	1-31
	No: Claims	32-62

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject matter of claims 32-62 concerns a method of treatment of the human/animal body which is considered by this Authority to be covered by the provisions of Rule 67.1 (IV) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of this claim (Article 34(4) (a)(I)PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this communication:

D1 : WO 96/40116 A (SUGEN, INC) 19 December 1996 (1996-12-19) cited in the application

D2 : WO 03/002107 A (AB SCIENCE; MOUSSY, ALAIN; KINET, JEAN-PIERRE) 9 January 2003 (2003-01-09)

2. For the assessment of the present claims 32-62 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Inventive step

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 1-62 does not involve an inventive step in the sense of Article 33(3)PCT. Document D2, which is considered to represent the most relevant state of the art, discloses the utility of tyrosine kinase inhibitors for treating multiple sclerosis. The subject-matter of claims 1-62 differs from the disclosure of D2 in that the compounds used for the same purpose are the indolinone derivatives of formula I. The problem to be solved by the present invention may therefore be regarded as finding an alternative treatment of multiple sclerosis. D1 discloses the compounds of the present invention as known tyrosine kinase inhibitors

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useful in therapy, for example for treating a number of diseases such as neurodegenerative diseases, which are diseases related to abnormalities in receptor tyrosin kinase. Therefore, being aware that tyrosine kinase inhibitors are useful for treating and preventing multiple sclerosis, and knowing that the compounds of formula 1 are tyrosine kinase inhibitors, the person skilled in the art would have been inevitably led to use the indolinone derivatives of formula 1 of the present invention for treating the claimed disorder. Due to their well known tyrosine kinase inhibitor activity, the skilled person would have expected for the compounds of formula 1 the same effect on multiple sclerosis as the tyrosine kinase inhibitors described in document D2.